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10/567,992	10/04/2006	Russell John Stewart	00846-U3051.PCT.US	5509
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THORPE NORTH & WESTERN, LLP. P.O. Box 1219 SANDY, UT 84091-1219			EXAMINER	
			KOSAR, AARON J	
ART UNIT		PAPER NUMBER		
1651				
NOTIFICATION DATE		DELIVERY MODE		
01/20/2011		ELECTRONIC		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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<b>Office Action Summary</b>	<b>Application No.</b> 10/567,992	<b>Applicant(s)</b> STEWART ET AL.
	<b>Examiner</b> AARON J. KOSAR	<b>Art Unit</b> 1651

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 01 November 2010.  
 2a) This action is FINAL.      2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-79 is/are pending in the application.  
 4a) Of the above claim(s) 30 and 45-79 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-29 and 33-44 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-442)  
 3) Information Disclosure Statement(s) (PTO-SB/08)  
     Paper No./Mail Date 3/8/2007
- 4) Interview Summary (PTO-413)  
     Paper No./Mail Date \_\_\_\_\_  
 5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_

**DETAILED ACTION**

**Election/Restrictions**

Applicant's election without traverse of Group I and the species (A) oxidation agent activating coordination complex, (B) nickel, (C,D) protein/PEG/biotin, (E) silica solid surface, and (G) peroxidase in the reply filed on 11/1/2010 is acknowledged.

The requirement is still deemed proper and is therefore made FINAL.

Claims 45-79 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Claim 30 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/1/2010.

Claims 1-29 and 31-44 are pending and have been examined on the merits.

### **Drawings**

The drawings are objected to because in figure 5, the composition "H<sub>6</sub>H6GYGY-titin I28" appears to be a typographical error of the compound -- H<sub>6</sub>GYGY-titin I28--.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

**Claim Rejections - 35 USC § 112**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-29 and 31-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 at each of lines 3 and 4, the claim recites the phrase "a metal ligand"; however it is unclear if Applicant intends for the metal ligands to be the same or different metal ligands. Clarification is required.

In claim 1, the claim recites attaching "a metal ligand" to a "first moiety" and a "second moiety" at lines 3-4 and recites the phrase "phenolic groups or phenolic derivatives attached to each of the first and second moieties" at lines 7-8; however, it is unclear in the method if the metal ligand(s) is/are the same as or different from the phenolic groups and/or derivatives. Furthermore, because it is unclear what component or fragments thereof Applicant intends for to qualify or exclude from functioning as a ligand, moiety, and/or phenolic, then the physical measurements thereof (molecular weights, atomic distances, degree of polymerization thereof) and the correspondence to and intended arrangement of the elected species within the method, then the claims also cannot clearly distinguish the claimed method and species therein from the materials, weights, and distances intrinsic to the prior art methods. Clarification is required.

In claim 1 at lines 6-8 the claims recites the phrase “which in the presence of an oxidizing agent leads to the formation of at least one covalent crosslink between phenolic groups or phenolic derivatives attached”; however, it is unclear if an oxidation agent, crosslinking, or a cross-linked product are required or are merely exemplary in the method. Clarification is required.

In claim 21 the claim recites the term “small”; however, the claims (except for claims 22 and 25) do not further define the term, the specification does not provide an objective measure by which one would determine a molecule as qualified as or excluded from being small, and one of skill would not be apprised as to what Applicant intends by the term. Clarification is required.

In claim 25 the claim recites the phrase the group “consisting of...and derivates thereof”; however, the term “derivatives” extends the scope of the phrase “consisting of” to expand to a limitless number of additional compounds not limits, and thus the metes and bounds of the claim are unclear. Clarification is required. Please note, however, this ground maybe be overcome for example by cancelling the phrase “and derivatives thereof”, or by other appropriate amendment.

In claims 40-42, the claims recite the terms “HY-tag”, “CY-3”, and “CY-5”; however it is unclear what Applicant intends by the terms. Please note, however, if Applicant intends for example, an abbreviation of a “His-Tyr tag (HY tag)” and “a CY-3 or CY-5 fluorescent label”, then the claims in the first instance in the claims should indicate the expanded terms adjacent to the abbreviated terms. Clarification is required.

All other claims depend directly or indirectly from the rejected claims and are, therefore, also rejected under 35 USC § 112, second paragraph, for the reasons set forth above.

#### **Claim Rejections - 35 USC § 102/103**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 12-18, 21-23, 25, 26, 27, 29, 31, 37, 38, 43, and 44 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Ho et al (Langmuir 1998, 14(14), 3889-3894).

The claims are drawn to a method comprising attaching a metal ligand to a first moiety, a metal ligand to a second moiety, and adding a metal ion to form a coordination complex between the first and second moiety. Although the reference of Ho et al does not teach the elected species combination, it demonstrates the non-allowability of the generic invention as follows.

The cited reference discloses a method comprising forming a nitrilotriacetic acid (NTA) chelate composition (attaching carboxylate metal ligands to moieties of the nitrogen-containing core compound; bio/synthetic polymers; small molecule (e.g. NH<sub>3</sub><sup>+</sup> group) derivative of e.g. biotin) and then adding to the NTA Ni<sup>+2</sup>, which appears to be identical to the presently claimed composition since it requires in the method the same materials and produces the same product as instantly claimed. The cited reference further teaches that the composition is further tethered to a polymer bead (solid surface, polystyrene (PS)). Consequently, the claimed method appears to be anticipated by the reference.

In the alternative, even if in the method the composition(s) therein (with respect to the attaching mode or structural features/components/arrangements thereof; the ability to participate in some intended use such as a enzyme activation or an oxidation reaction resulting in phenolic group addition and/or reaction to provide crosslinking thereof) is not identical to the referenced method's composition(s), with regard to some unidentified characteristics, the differences between that which is claimed and that which is disclosed, is so slight that the referenced

method's composition is likely to inherently possess the same characteristics of that instantly claimed, particularly in view of the similar characteristics which they have been shown to share (e.g. providing ligands, moieties, metal ions and forming (coordination) a metal ion (nickel) complex therewith)(see. entire document, for example, page 3890 line 4; figure 2; page 3891 lines 8-9). Thus, the claimed composition would have been obvious to those of ordinary skill in the art within the meaning of 35 USC § 103(a).

Accordingly, the claimed invention as a whole was at least *prima facie* obvious, if not anticipated by the reference, especially in the absence of sufficient, clear, and convincing evidence to the contrary.

### **Claim Rejections - 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

- (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-24, 26, 27 and 31-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gill et al ("Nickel-dependent oxidative cross-linking of a protein" Chem. Res. Toxicol. March 1997, 10(3), 302-9.).

The claims are drawn to a method comprising attaching a metal ligand to a first moiety, a metal ligand to a second moiety, and adding a metal ion to form a coordination complex between the first and second moiety.

Gill teaches that a method comprising forming by the action of horseradish peroxidase (metalloenzyme) and H<sub>2</sub>O<sub>2</sub> (oxidant), and which is known to couple proteins (first and second moieties) via formation of dityrosine (phenolic metal ligands added to the first and second moieties; covalent crosslink), and that free Ni<sup>2+</sup> (metal ion) intrinsically and spontaneously binds to peptide backbones, creating metal-peptide sites (to form a coordination complex between the 1<sup>st</sup> and 2<sup>nd</sup> moieties) which are sensitized to oxidants (see entire document, e.g. page 303, left column lines 28-30 and right column lines 47-51).

Although Gill does not recite a metal-to-phenolic distance for the nickel complex, it is would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to have provided the claimed dimensions, because it is deemed that the metal

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coordination to tyrosine as taught by Gill would intrinsically provide a Ni-O bond length or Ni:phenolic group distance as instantly claimed. Gill further teaches that providing nickel metal ion,  $\text{Ni}^{+2}$ , to bovine RNase (adding metal ion to first and second moieties containing metal ligands; polymers/biopolymers/ small molecules) forms multimeric products, including dimers, trimers and higher oligomers thereof (coordination complex, covalent/oxidative crosslinked compound)(e.g. page 303, left column lines 33-38 and right column "Results"). Although Gill does not expressly recite adding metal ligand(s) to a first or second moieties, since Gill teaches that the RNase in the method is obtained from bovine source and said bovine source would necessarily synthesizes the tyrosine-containing (phenolic group or phenolic derivative; tyrosine containing moieties) RNase protein sequence, then obtaining the protein from a bovine source would inherently comprise adding a tyrosine (phenolic group or derivative) ligand to each of a first and second moieties (see entire document, e.g. page 303 "Materials").

Claims 1-24, 26-29 and 31-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stewart et al (U.S. Patent No. 6,087,452) in view of Fancy et al ("A Critical Role for Tyrosine Residues in His<sub>6</sub>Ni-Mediated Protein Cross-Linking" Biochem. Biophys. Res. Comm. 1998, 247, 420-426.).

Stewart et al teaches a method of making a substrate-immobilized composition which said method comprises adding acetic acid (attaching metal ligands) to lysine (first, second moieties) to form a nitrilotriacetic acid (NTA) compound (see entire document, e.g. column 8). Stewart teaches that the compound is contacted with  $\text{Ni}^{+2}$  (metal coordination complex) (e.g.

column 9 lines 20-24) and that the complex is further coordinated to polystyrene (PS) beads having added luciferase (metal ligand; phenolic group-, derivative-, nucleophilic/electron donating group-, and tyrosine-containing protein; metalloenzyme)(e.g. column 9 lines 9-24).

Stewart and the instant claims differ in that Stewart does not expressly recite providing horseradish peroxidase (HRP) or crosslinking tyrosine/phenolic groups.

It would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to have provided in the method of Stewart with tyrosinyl residues (phenolic group or derivative) because Stewart teaches (ii) that the metal in the method coordinates with groups, including histidinyl tags and any other tags which are "free to bond with electron-donating or metal-affinity side chains" and that (ii) the reaction may be with a difunctional compound (e.g. a poly-His tag) or by co-reaction of the metal chelate with more than one protein wherein each protein contains metal affinity tags (e.g. adding the metal ion-containing chelate to a mixture of tagged proteins) (e.g. column 3 line 46 - column 4 line 7; column 4 lines 43-48).

Furthermore, as taught by Fancy et al, providing Tyr-to-a His<sub>6</sub> tags (forming a HY-tag), coordinating the HY-tags with a nickel ion (a metal ion, nickel), and cross-linking the Tyr hydroxyl (OH) residues with horse radish peroxidase (HRP) provides a fluorescently detectable cross-linked dityrosine (see entire document, e.g. page 420, abstract, lines 1 through 29; page 421 lines 17-38). Thus one would have been motivated to have provided the method of Stewart with dityrosine groups because one seeking to monitor the coupling reaction of Stewart would recognize from the teachings of Fancy that the oxidative coupling to form dityrosine provides a measurable nickel-enhanced fluorescence in the method. One would have had a reasonable expectation of success because success merely requires tyrosine tagging the compositions in the

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method of Stewart with the tyrosine of Fancy and reacting the compounds to obtain the covalently cross-linked dityrosinyl group, by reactions known to the person of ordinary skill as taught by Fancy and Stewart and especially in the absence of objective evidence to the contrary.

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

No claims are allowed.

**Conclusion**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AARON J. KOSAR whose telephone number is (571)270-3054. The examiner can normally be reached on Monday-Thursday, 7:30AM-5:00PM, ALT. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Aaron J Kosar/  
Examiner, Art Unit 1651

/Christopher R. Tate/  
Primary Examiner, Art Unit 1655